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EXAMINER
EPPERSON, JON D

ART UNIT	PAPER NUMBER
1639	20

DATE MAILED: 12/23/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
File Copy	09/518,813	JOSEPH ET AL.	
	Examiner	Art Unit	
	Jon D Epperson	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 March 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11,14,15,26-42 and 57* is/are pending in the application.

4a) Of the above claim(s) *6,9,14,26 and 57* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,7,8,10,11,15 and 27-42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☒ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Please note: The Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to **Group Art Unit 1639**. Please also note the change in Examiner.

Please note: The Examiner respectfully requests an updated copy of all pending claims.

Status of the Application

1. Receipt is acknowledged of a response to a restriction requirement, which was dated on March 20, 2002 (Paper No. 13).

Status of the Claims

2. Claims 1-11, 14-15, 26-42 and 57 are pending in the present application. Please note that claims 24 and 25 were withdrawn from consideration when applicant elected Group I without traverse in Paper No. 10 i.e., see page 2, "Applicants hereby provisionally elect Group I, Claims 1-15, 26-42, and 57..." Therefore, claims 24 and 25 are NOT pending in the present application as mistakenly indicated in the Supplemental Restriction Requirement dated on November 20, 2001 (Paper No. 11, page 2, paragraph 1) and in the Response to the Supplemental Restriction Requirement (Paper No. 13, page 1, paragraph 1).

3. Applicant's response to the Restriction and/or Election of Species requirements in Paper No. 13 is acknowledged and claim 57 is withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected inventions, there being no allowable generic or linking claim (see below i.e., ***Response to Restriction and/or Election of Species***).

4. Claims 6, 9, 14, 26 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected species (see below i.e., ***Response to Restriction and/or Election of Species***).

5. Therefore, claims 1-5, 7-8, 10-11, 15, 27-42 are examined on the merits in this action. Please note that claims 1-5, 7-8, 10-11, 15, 27-42 are only examined to the extent of the elected species and/or subject matter (see MPEP § 803.02).

Response to Restriction and/or Election of Species

6. Applicant's election of Group I (claims 1-11, 14-15 and 26-42) in Paper No. 13 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

7. Applicant's election of species in Paper Nos. 10 (i.e., in vitro transcription and translation) and 13 (i.e., binding to protein, polypeptide, HIV tat, streptavidin, immobilized, glass slide) is also acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election of species has also been treated as an election without traverse (MPEP § 818.03(a)).

8. As a result, the restriction requirement and/or election of species is still deemed proper and is therefore made **FINAL**.

Information Disclosure Statement

9. The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98 (b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on the form PTO-892, they have not been considered.

10. The references listed on applicant's PTO-1449 form have been considered by the Examiner. A copy of the form is attached to this Office Action.

Specification

11. The oath or declaration is missing. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

Claims Rejections - 35 U.S.C. 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

12. Claims 1-5, 7-8, 10-11, 15, 27-42 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. For **claims 1-2**, the use of the term "can" is vague and indefinite. For example, it is not clear whether applicant is describing a screening method or not. Are the proteins being synthesized screened or aren't they? Is applicant is describing two different methods (that might need to be further restricted) wherein one method entails screening and the other method does not? Consequently, the metes and bounds of the claimed invention cannot be determined. Therefore, claims 1-2 and all dependent claims are rejected under 35 U.S.C. 112, second paragraph.

B. For **claim 1**, the entire claim is vague and indefinite. For example, it is not clear what "can" be screened? Does applicant intend for the "synthesized individual proteins" to be screened or some other proteins that have nothing to do with the gene library i.e., the actual proteins that "can" be screened are not specified. Therefore, claim 1 and all dependent claims are rejected under 35 U.S.C. 112, second paragraph.

C. For **claims 1, 3, 4, 7, 15, 27, 37** the term "gene library" is vague and indefinite. For example, it is not clear what types of libraries would be encompassed by a "gene library"? Does applicant intend for the library members to be isolated from cellular genes or can they be synthesized via solid-phase synthesis? What if the synthesized sequence is identical to the one derived from a gene, would it qualify as a "gene library"? What if some of the library members do not come from a gene, but others do, would the

collection still be considered part of a "gene library"? What if none of the sequences were derived from a gene, but were subsequently incorporated into genes, would they be considered apart of a "gene library"? Furthermore, the term "gene" implies a DNA sequence that exists in nature and includes coding, non-coding regions, as well as all regulatory sequences associated with expression. This does not appear to be Applicant's intention, as evidenced by the claims drawn to "gene libraries" derived from mRNA. It is suggested that "gene" be replaced with "polynucleotide". Consequently, the metes and bounds of the claimed invention cannot be determined. Therefore, claim 1, 3, 4, 7, 15, 27, 37 and all dependent claims are rejected under 35 U.S.C. 112, second paragraph.

D. For **claim 1**, the it is not clear whether the "synthesi[zed] individual proteins" are derived from the gene library or not. The claim simply states that a gene library is formed AND proteins are synthesized. The close proximity of the two phrases seems to imply that the proteins were derived from the gene library, but this is not specifically stated in the claim. Clarification and/or correction is requested. Consequently, claim 1 and all dependent claims are rejected under 35 U.S.C. 112, second paragraph.

E. For **claim 3**, the term "derived from" is vague and indefinite. For example, it is not clear how the gene library is "derived from" the mRNA. Is the mRNA synthetically converted into the DNA by a series of chemical transformations? Is the mRNA reverse transcribed to make cDNA? Is the mRNA broken into pieces, reverse transcribed, and amplified to make the members of the library? Is the mRNA degraded into single nucleotides and used in *in vitro* transcription reactions on another DNA template and then reverse transcribed? Consequently, the metes and bounds of the claimed invention

cannot be determined. Therefore, claims 3 and all dependent claims are rejected under 35 U.S.C. 112, second paragraph.

F. For **claims 4, 10, 35**, the phrase "such as" renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d). Therefore, claim 4 and all dependent claims are rejected under 35 USC 112, second paragraph.

G. For **claim 4**, the phrase "library of variable molecules" is vague and indefinite. For example, it is not clear when a "library" would ever NOT be composed of "variable" molecules? Applicants are requested to clarify and/or correct. Consequently, claim 4 and all dependent claims are rejected under 35 U.S.C. 112, second paragraph.

H. For **claim 10**, the phrase "wherein solid phase is a contiguous surface" is vague and indefinite. For example, it is not clear if the solid phase could ever be anything other than a "contiguous surface"? Applicants are requested to clarify and/or correct. Consequently, claim 10 and all dependent claims are rejected under 35 U.S.C. 112, second paragraph.

I. **Claims 15, 27, 37** recite the limitation "the nucleic acid." There is insufficient antecedent basis for this limitation in the claim. Therefore, claims 15, 27, 37 and all dependent claims are rejected under 35 USC 112, second paragraph.

J. **Claim 15, 27, 37** recites the limitation "each clone." There is insufficient antecedent basis for this limitation in the claim. Therefore, claim 15, 27, 37 and all dependent claims are rejected under 35 USC 112, second paragraph.

K. For **claims 27-29**, the use of the term "permits" is vague and indefinite. For example, it is not clear when isolation of the target cell would ever not be "permitted"? There is nothing "preventing" a researcher from isolating a target cell. Is applicant referring to governmental regulations that would not legally "permit" the isolation of prohibited substances? Clarification and/or correction is requested. Therefore, claims 27-29 and all dependent claims are rejected under 35 U.S.C. 112, second paragraph.

L. **Claims 27-29, 38** recite the limitation "the displayed protein or polyeptide." There is insufficient antecedent basis for this limitation in the claim. Therefore, claims 27-29 and 38 and all dependent claims are rejected under 35 USC 112, second paragraph.

M. **Claims 27** recite the limitation "the one or more protein or polyeptide." There is insufficient antecedent basis for this limitation in the claim. Therefore, claim 27 and all dependent claims are rejected under 35 USC 112, second paragraph.

N. For **claim 29**, the phrase "wherein binding to the target cell results in an alteration to the target cell which then permits isolation of the target cell and recovery of genes encoding the displayed protein or polypeptide" is vague and indefinite. For example, it is not clear what is "binding" to the target cell? Is the "displayed protein or polypeptides" binding to the target cell or is it some other molecules? Consequently, the metes and bound of the claimed invention cannot be determined. Therefore, claim 29 and all dependent claims are rejected under 35 U.S.C. 112, second paragraph.

O. **Claim 30** recites the limitation "the complex" in the last line. There is insufficient antecedent basis for this limitation in the claim. Therefore, claim 30 and all of

the claims from which claim 30 depends are rejected under 35 USC 112, second paragraph.

P. For **claim 31**, the phrase "subsequent viability" is vague and indefinite. For example, it is not clear what the viability is "subsequent" to? Is the viability "subsequent" to the production of molecules produced by the target cell i.e., the living microorganism cannot grow without said molecules i.e., the molecules represent some sort of growth nutrient? Does the term "subsequent viability" represent some sort of "birth"? Furthermore, viability is a relative term, which further renders the claim indefinite and unclear. Can the cells be more or less viable over time? Consequently, the metes and bound of the claimed invention cannot be determined. Therefore, claim 31 and all dependent claims are rejected under 35 U.S.C. 112, second paragraph.

Q. **Claims 27, 33-34, 40** recites the limitation "the cell." There is insufficient antecedent basis for this limitation in the claim. The Examiner suggests "the target cell." Therefore, claims 27, 33-34, 40 and all dependant claims are rejected under 35 USC 112, second paragraph.

R. For **claims 35-36**, the term "derived from" is vague and indefinite. For example, it is not clear how the molecule is "derived from" the target cell? Is the molecule secreted by the target cell, displayed on the target cells surface, secreted or displayed as a precursor, produced in final form or as a precursor only as a result of the cell's death after external forces have broken it down? Consequently, the metes and bounds of the claimed invention cannot be determined. Therefore, claims 35-36 and all dependent claims are rejected under 35 U.S.C. 112, second paragraph.

S. For **claim 39**, the phrase "which can function as all or part of a label or can initiate a labeling reaction" is vague and indefinite. For example, it is not clear how a molecule could acts as "part of a label"? Applicants are requested to clarify and/or correct. Therefore, claim 39 and all dependent claims are rejected under 35 U.S.C. 112, second paragraph.

T. **Claim 37** recites the limitation "the synthesized proteins or polypeptides." There is insufficient antecedent basis for this limitation in the claim. The Examiner suggests "the target cell." Therefore, claims 37 and all dependant claims are rejected under 35 USC 112, second paragraph.

U. For **claim 37**, the phrase "bringing one or more of the synthesized proteins or polypeptides into the vicinity of a modified ligand which bind to a receptor on the surface of a cell or tissue to label the synthesized proteins or polypeptides on the cell/tissue surface" is vague and indefinite. It is just not clear what applicant intends by this statement? First, what is binding to the receptor? Is it the synthesized proteins or polypeptides or the modified ligand? Second, the phrase "label the synthesized proteins or polypeptides on the cell/tissue surface" seems to contradict the prior statement in the claim and parent claims because the "ligand" is supposed to be bound to the cells not the "synthesized proteins." Furthermore, does bringing one or more of the synthesized proteins or polypeptides "into the vicinity" of a modified ligand mean that they bind to said ligand and if not what is doing the binding here? Applicants are requested to clarify and/or correct. Furthermore, the phrase "into the vicinity" is a relative term, which further renders the claim indefinite. Does "into the vicinity" mean in the same lab space?

test tube? Are the two able to chemically interact with one another and if so do they bind? Consequently, the metes and bounds of the claimed inventions cannot be determined. Therefore, claim 37 and all dependent claims are rejected under 35 U.S.C. 112, second paragraph.

V. **Claim 41** is recited in improper Markush format. The claim uses more than one "or" in the list i.e., "or protein binding molecule ... or nickel." It is suggested to use standard Markush language; see MPEP 2173.05(h) concerning alternative expressions:

> Alternative expressions are permitted if they present no uncertainty or ambiguity with respect to the question of scope or clarity of the claims. One acceptable form of alternative expression, which is commonly referred to as a Markush group, recites members as being "selected from the group consisting of A, B and C." See Ex parte Markush, 1925 C.D. 126 (Comm'r Pat. 1925).
>
> When materials recited in a claim are so related as to constitute a proper Markush group, they may be recited in the conventional manner, or alternatively. For example, if "wherein R is a material selected from the group consisting of A, B, C and D" is a proper limitation, then "wherein R is A, B, C or D" shall also be considered proper.

Therefore, claims 41 and all dependent claims are rejected under 35 U.S.C. 112, second paragraph.

Claims Rejections - 35 U.S.C. 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

13. Claims 1-5, 7-8, 10-11, 15, 27-28, 30, 34, 37-39 and 42 are rejected under 35 U.S.C. 102(b) as being anticipated by Johnstone et al (Johnstone, A.; Thorpe, R. *Immunochemistry in Practice*. Blackwell Scientific Publications, Oxford, England, **1987**).

For ***claim 1***, Johnstone et al discloses a method for the high throughput screening of a large population of host cells (in this case hybridoma cells derived from the fusion of spleen cells from an immune animal with neoplastic B cells) for the production of monoclonal antibodies, which anticipates claim 1 (see Johnstone et al, pages 35-41 and 241-246, especially page 35, first paragraph and page 39, section 2.3.2, first paragraph). In this scenario, the antibodies that are produced by the hybridoma cells (derived from the immunized animal) represent the "proteins or polypeptides" that are being "screened" and the collection of genes that encode said antibodies represent the "gene library" that is produced after immunization. Selecting "favorable" hybridoma cells after several rounds of "screening" results in the production of monoclonal antibodies i.e., results in the "synthesis" of individual proteins that are derived from the gene library (see Johnstone et al, page 39-42, note 7 on page 39 and section 2.3.2) (see also Johnstone et al, page 39, section 2.3.2, first paragraph, and page 40, section 2 on "Cloning by limiting dilution", first paragraph) ("Cloning is the process by which an individual cell is isolated and allowed to grow into a homogenous colony of cells [in this case the cells are grown and screened for monoclonal antibody production on 96-well microtitre plates]. Cloning should be carried out 2-3 times to ensure that the antibody is monoclonal [this requires each position to be assayed and the wells that contain the "desired molecule" i.e., monoclonal antibody are selected for and used in a second/third round of cloning]").

For ***claim 2***, Johnstone et al also discloses screening the secreted antibodies using radiobinding immunoassays, immunofluorescence microscopy or flow microfluorimetry analysis (see Johnstone et al, page 39, note 7; see also page 241-248), which anticipates claim 2. For example, figure 11.1 (see Johnstone et al, page 242) shows a schematic representation of antibody that is secreted from the hybridoma cells (i.e., the "individual" protein or polypeptide of claim 2) binding to an immobilized antigen (i.e., "one or more" other molecules/ligands).

For ***claim 3***, Johnstone et al discloses antibodies that were "synthesized" by hybridoma cells i.e., derived from the mRNA of one or more hybridoma cells via transcription and translation (see Johnstone et al, page 35, section 2.3 and page 39, section 2.3.2), which anticipates claim 3.

For ***claim 4***, Johnstone et al discloses screening hybridoma cells for the production of monoclonal antibodies (see Johnstone et al, page 35, section 2.3 and page 39, section 2.3.2), which anticipates claim 4 because monoclonal antibodies contain "antibody variable regions."

For ***claim 5***, Johnstone et al discloses that the antigens that bind to the monoclonal antibodies can be proteins or peptides from a cell or tissue (see Johnstone et al, page 244, section 11.1.2; see also page 247, paragraph 4; see also page 248, Table 11.1), which anticipates claim 5.

For **claim 7**, Johnstone et al also discloses a method whereby the host cells are arranged in a "spatial array so each position in the spatial array is occupied by one cell" (see Johnstone et al, page 40, section 2 on "Cloning by limiting dilution", first paragraph)

("The cells are plated out at theoretical concentrations of 1 cell/well ... us[ing] 96-well microtitre plates"), which anticipates claim 7 because the arrayed cells each produce one or more protein or polypeptides i.e., they each produce one or more antibodies

For ***claims 8 and 10***, Johnstone et al discloses solid phase radioimmunoassays on microtitre plates i.e., multi-well plates (see Johnstone et al, page 246, section 11.2), which anticipates claims 8 and 10 because the antibodies are first coupled to a solid support at specific loci before they are screened with antigen (see also page 247, last paragraph) ("The use of solid-phase techniques involving antibody bound to microtitre plates, plastic tubes, beads (most recently magnetic; Amersham – Appendix 3) or some other solid support ... simplifies the separation of free an bound antigen"). Johnstone et al also discloses a method for the screening of a large population of host cells for the production of a molecule of interest using a "microtiter plate"(see Johnstone et al, page 40, section 2 on "Cloning by limited dilution", first paragraph) ("The method [for screening host cells] ... uses 96 well microtiter plates").

For ***claim 11***, Johnstone et al discloses the production of monoclonal antibodies via a cloning process wherein hybridoma cells are grown outside the body on microtiter plates and said antibodies are produced by transcription and translation, which anticipates claim 11 (see also Johnstone et al, page 39, section 2.3.2, first paragraph, and page 40, section 2 on "Cloning by limiting dilution", first paragraph) ("Cloning is the process by which an individual cell is isolated and allowed to grow into a homogenous colony of cells [in this case the cells are grown and screened for monoclonal antibody production on 96-well microtitre plates]. Cloning should be carried out 2-3 times to ensure that the

antibody is monoclonal [this requires each position to be assayed and the wells that contain the "desired molecule" i.e., monoclonal antibody are selected for and used in a second/third round of cloning]"), which anticipates claim 11.

For ***claims 15, 27 and 37***, Johnstone et al discloses a method for the high throughput screening of a large population of host cells (in this case hybridoma cells derived from the fusion of spleen cells from an immune animal with neoplastic B cells) for the production of monoclonal antibodies (i.e., production of moloclonal antibodies would fall within the category of a "biological phenotype"), which anticipates claims 15 27, and 37 (see Johnstone et al, pages 35-41 and 241-246, especially page 35, first paragraph and page 39, section 2.3.2, first paragraph). In this scenario, the antibodies that are produced by the hybridoma cells (derived from the immunized animal) represent the "proteins or polypeptides" that are being "screened" and the collection of genes that encode said antibodies represent the "gene library" that is produced after immunization. Selecting "favorable" hybridoma cells after several rounds of "screening" results in the production of monoclonal antibodies i.e., results in the "synthesis" of individual proteins that are derived from the gene library. Furthermore, Johnstone et al discloses the production of monoclonal antibodies via a cloning process wherein hybridoma cells are grown outside the body on microtiter plates and said antibodies are produced by transcription and translation i.e., said antibodies are produced by *in vitro* translation (see Johnstone et al, page 39-42, note 7 on page 39 and section 2.3.2) (see also Johnstone et al, page 39, section 2.3.2, first paragraph, and page 40, section 2 on "Cloning by limiting dilution", first paragraph) ("Cloning is the process by which an individual cell is isolated

and allowed to grow into a homogenous colony of cells [in this case the cells are grown and screened for monoclonal antibody production on 96-well microtiter plates]. Cloning should be carried out 2-3 times to ensure that the antibody is monoclonal [this requires each position to be assayed and the wells that contain the "desired molecule" i.e., monoclonal antibody are selected for and used in a second/third round of cloning]"). Finally, Johnstone et al discloses methods wherein said antibodies are screened with cells or tissues (see Johnstone et al, page 244, section 11.1.2).

For ***claims 28 and 30***, Johnstone et al discloses binding antibodies to target cells wherein the target cells are "altered" as a result of the binding i.e., the conformation of the antigens displayed on the target cells are "altered" when bound by antibodies via non-covalent dipole-dipole, charge-dipole interactions, etc. (see Johnstone et al, page 244, section 11.1.2; see also page 247, paragraph 4), which anticipates claim 28 because the type of "alteration" was not specified and the term "permitted" is vague and indefinite (see 35 U.S.C. 112, second paragraph rejection above). The isolation of target cell proteins and genes are always "permitted" since they were never "prevented" and, consequently, the addition of monoclonal antibodies continues to "permit" their isolation. Furthermore, Table 11.1 (see Johnstone et al, page 248) outlines many techniques that could be used to "permit" the isolation of said antigen and, consequently, said antigen bound cells e.g., via adsorption of free antigen on dextran coated charocal, ion exchange resins, etc. Finally, Johnstone et al also reads on the limitation wherein "the target cell binds to one or more of the components of the complex" as well because it is not clear what applicant is referring to by "the complex" (see 35 U.S.C. 112, second paragraph

rejection above) and because a "complex" is formed between antibody and antigen wherein the cell is attached to the antigen.

For ***claim 34***, Johnstone et al discloses the use of immunofluorescence microscopy for the detection of cell surface antigens (see Johnstone et al, page 245, first paragraph, see also section 12.2.4), which anticipates claim 34.

For ***claim 38***, Johnstone et al discloses the detection and isolation of cell surface antigens (see Johnstone et al, page 242, figure 11.1b), which anticipates claim 38.

For ***claim 39 and 42***, Johnstone et al discloses an ELISA assay (see Johnstone et al, page 257-8, section 11.4), which anticipates claims 39 and 42 because the ligand is a protein that is modified with an enzyme that can initiate a labeling reaction including "alkaline phosphatse, β-D-galactosidase and horseradish peroxidase" (see page 258, second paragraph).

14. Claims 1-5, 7-8, 10-11, 15, 27-32, 34-39 and 42 are rejected under 35 U.S.C. 102(e) as being anticipated by Ghai et al (US # 5,955,269) (Date of Patent: **Sep. 21, 1999**; Filed: **Jun. 20, 1996**).

For ***claim 1***, Ghai et al discloses a method for "screening foods and food substances which are capable of modulating the expression of one or more genes that are related to or associated with a disease or undesirable condition" (see Ghai et al, column 3, lines 40-45), which anticipates claim 1. For example, Ghai et al discloses producing a "gene library" wherein cultured test cells "containing a disease-related gene or portion thereof' are contacted (i.e., screened) with a particular food or food substance (see Ghai

et al, column 4, line1) (see also column 4, lines 58-64, "In another embodiment, the methods of the invention can be used to test the effect of a particular food or food substance on a variety of diseases or undesirable conditions. In this instance, a panel of disease-related genes contained in one or more test cell lines [i.e., a gene library] are used to analyze whether expression of the genes is modulated by the food or food substances in question") (see also columns 11-17, section for "Test Cells and Gene Expression Systems") (see also columns 6-11, section for Genes Associated with Diseases or Undesirable Conditions). Furthermore, Ghai et al discloses a variety of assay techniques used to screen the "synthesized individual proteins" from the "gene library" including protein assays (see Ghai et al, column 4, lines 20-32, "Expression of he disease-related genes may be achieved by assaying, in a cell lysate, the level of messenger RNA of the disease-related gene (e.g., by Northern blot analysis), or the level of functional activity of the disease-related gene product (e.g., by Western blot analysis). If the disease-related gene product is secreted, the culture media can be assayed for the level or functional activity of the disease related gene product") (see also columns 19-21, especially column 19, lines 44-60) ("The present invention also provides proteins based screening assays which are based on the physical, immunological or functional properties of the gene product, report molecule, fusion protein or metabolite").

For ***claim 2***, Ghai et al also discloses Western blotting to screen disease-related gene products (see Ghai et al, column 4, lines 24), which anticipates claim 2 because it shows the "synthesized" proteins or polypeptides binding to other molecules e.g., antibodies, etc. (see also columns 17-22, section for "Screening Assays", see especially

columns 19-22 on protein assays and in particular column 19, last two paragraphs "The present invention also provides protein-base screening assays which are based on the physical, immunological or functional properties of the gene product, reporter molecule, fusion protein or metabolite ... Antibodies, or fragments of antibodies, such as those described below can be used to quantitatively or qualitatively detect by immunospecific binding the presence of disease-related gene product, reporter molecule, fusion protein or metabolite").

For ***claim 3***, Ghai et al also discloses a method wherein the gene library is constructed from cDNA, which anticipates claim 3 because cDNA is made from mRNA via reverse transcription (see Ghai et al, column 12, lines 40-42, "The disease-related gene can also be complementary DNA (cDNA) or portions thereof. Any allelic, variant, polymorphic or mutant form of a disease-related gene can be used in the screening assay") (see also column 18, lines 61-62 for definition of cDNA).

For ***claim 4***, Ghai et al also discloses a gene library that may contain "[a]ny allelic, variant, polymorphic or mutant form of a disease related gene" for the screening assay (see Ghai et al, column 12, lines 42-43), which anticipates claim 4 because the gene products of "allelic, variant, polymorphic or mutant forms" represent a library of "variable" molecules.

For ***claim 5***, Ghai et al also discloses binding the "synthesized" proteins or peptides to monoclonal antibodies (see Ghai et al, column 19, lines 61-64), which anticipates claim 5 because the monoclonal antibodies were produced by "cells" i.e., hybridoma cells (see Ghai et al, column 20, lines 58-61).

For **claim 7**, Ghai et al also discloses a method whereby the host cells are arranged in a "spatial array so each position in the spatial array is occupied by one cell", which anticipates claim 7 (see Ghai et al, column 17, lines 19-30) ("Test cells of the invention are maintained and handled by standard cell culture procedures. To facilitate high throughput screening, the test cells can be cultured and assayed in multi-well plates in an ordered array") (see also Ghai et al, column 11, lines 38-42, describing the use of clones [which are derived from a single cell] for high thorough put screening). Furthermore, Ghai et al also discloses assaying each array position for production of the molecule of interest and selecting the cells from those positions where the molecule was produced (see Ghai et al, column 29, lines 39-67, showing an example wherein the molecule of interest that is screened for is the enzyme lysyl oxidase (LOX)) ("the effect of several food substances ... on the transcriptional activity of the human lysyl oxidase gene [Lysyl oxidase enzyme] was assayed"). Furthermore, Ghai et al also discloses a method for the screening of a large population of host cells for the production of a molecule of interest using a solid surface (see Ghai et al, column 17, lines 18-24) ("To facilitate high throughput screening, the test cells can be cultured and assayed in multi-well plates in an ordered array").

For ***claim 8***, Ghai et al also discloses a method for the screening of a large population of host cells for the production of a molecule of interest wherein the spatial array is occupied by a bead (see Ghai et al, column 20, lines 19-40) ("The biological sample can be brought in contact with and immobilized onto a solid phase support ... which is capable of immobilizing cells) (By "solid phase support or carrier" is intended

any support capable of binding an antigen or an antibody [including] ... polystyrene beads"), which anticipates claim 8.

For **claim 10**, Ghai et al discloses, that the solid support can be "any" support capable of binding an antigen or an antibody, which would encompass a solid phase with a contiguous surface (see Ghai et al, column 20, especially lines 18-42, "The biological sample can be brought in contact with and immobilized onto a solid phase support or carrier such as nitrocellulose, or other solid support which is capable of immobilizing cells, cell particles or soluble proteins ... By "solid phase support or carrier" is intended any support capable of binding an antigen or an antibody. Well-known support or carriers include glass, polystyrene ... The support material can have virtually any possible structural configuration"). Therefore, claim 10 is anticipated.

For ***claim 11***, Ghai et al discloses culturing test cell used for screening in vitro (see Ghai et al, column 17, lines 18-24, "Test cells of the invention are maintained and handled by standard cell culture procedures. To facilitate high throughput screening, the test cells can be cultured and assayed in multi-well plates in an ordered array [i.e., in vitro]"), which anticipates claim 11 because the transcription and translation is occurring outside the body.

For ***claim 15***, Ghai et al discloses a method for "screening foods and food substances which are capable of modulating the expression of one or more genes that are related to or associated with a disease or undesirable condition" (see Ghai et al, column 3, lines 40-45), which anticipates claim 1. For example, Ghai et al discloses producing a "gene library" wherein cultured test cells "containing a disease-related gene or portion

thereof" are contacted (i.e., screened) with a particular food or food substance (see Ghai et al, column 4, line1) (see also column 4, lines 58-64, "In another embodiment, the methods of the invention can be used to test the effect of a particular food or food substance on a variety of diseases or undesirable conditions. In this instance, a panel of disease-related genes contained in one or more test cell lines [i.e., a gene library] are used to analyze whether expression of the genes is modulated by the food or food substances in question") (see also columns 11-17, section for "Test Cells and Gene Expression Systems") (see also columns 6-11, section for Genes Associated with Diseases or Undesirable Conditions). Furthermore, Ghai et al discloses a variety of assay techniques used to screen the "synthesized individual proteins" from the "gene library" including protein assays (see Ghai et al, column 4, lines 20-32, "Expression of he disease-related genes may be achieved by assaying, in a cell lysate, the level of messenger RNA of the disease-related gene (e.g., by Northern blot analysis), or the level of functional activity of the disease-related gene product (e.g., by Western blot analysis). If the disease-related gene product is secreted, the culture media can be assayed for the level or functional activity of the disease related gene product") (see also columns 19-21, especially column 19, lines 44-60) ("The present invention also provides proteins based screening assays which are based on the physical, immunological or functional properties of the gene product, report molecule, fusion protein or metabolite"). Furthermore, Ghai et al also discloses a method whereby the host cells are arranged in a "spatial array so each position in the spatial array is occupied by one cell", which anticipates claim 7 (see Ghai et al, column 17, lines 19-30) ("Test cells of the invention are maintained and handled by

standard cell culture procedures. To facilitate high throughput screening, the test cells can be cultured and assayed in multi-well plates in an ordered array") (see also Ghai et al, column 11, lines 38-42, describing the use of clones [which are derived from a single cell] for high thorough put screening). Furthermore, Ghai et al also discloses assaying each array position for production of the molecule of interest and selecting the cells from those positions where the molecule was produced (see Ghai et al, column 29, lines 39-67, showing an example wherein the molecule of interest that is screened for is the enzyme lysyl oxidase (LOX)) ("the effect of several food substances ... on the transcriptional activity of the human lysyl oxidase gene [Lysyl oxidase enzyme] was assayed"). Furthermore, Ghai et al also discloses a method for the screening of a large population of host cells for the production of a molecule of interest using a solid surface (see Ghai et al, column 17, lines 18-24) ("To facilitate high throughput screening, the test cells can be cultured and assayed in multi-well plates in an ordered array"). Finally, Ghai et al discloses performing assays "in situ", which would anticipate step (iv) of claim 15 wherein the arrays generated in (iii) are brought into "contact" with "one or more extracts from cells ... or with one or more cells ... per se" (see Ghai et al column 19, lines 33-43, "It is also possible to perform such disease-related gene expression assays "in situ", i.e., directly upon tissue sections ... Samples of tissue, can also be evaluated immunocytochemically using antibodies specific for the disease-related product or reporter molecule") (see also column 20, last paragraph, where hybridoma extracts are used for screening i.e., monoclonal antibodies).

For ***claim 27***, Ghai et al discloses a method for producing antibodies, chimeric antibodies and monoclonal antibodies against cells that contain genes that are associated with a disease wherein the level of production of said gene products is modulated by food or food substances (see Ghai et al, entire document, especially column 3, lines 41-52 and columns 20-21), which anticipates claim 27. In this scenario, the antibodies that are produced by the hybridoma cells and/or naturally occurring cells represent the "proteins or polypeptides" that are being "screened" and the collection of genes that encode said antibodies (and their hypervariable regions) represent the "gene library" that is produced after immunization. Selecting "favorable" hybridoma cells and/or natural cells after several rounds of "screening" results in the production of antibodies, monoclonal antibodies and/or chimeric antibodies that bind to the "target cells" that contain the genes associated with disease (see Ghai et al, column 20, paragraph s, "Immunoassays and non-immunoassays for disease-related gene products or reporter molecules will typically comprise incubating a sample; such as a biological fluid, a tissue extract, freshly harvested cells, test cell conditioned culture media or test cell lysates, in the presence of a detectably labeled antibody capable of identifying disease-related gene product or reporter molecule, and detecting the bound antibody by any of a number of techniques well known in the art") (see also column 21, lines 16-29, "Antibody fragments which recognize specific epitopes may be generated by known techniques ... Fab expression libraries can be constructed to allow rapid and easy identification of monoclonal Fab fragments with the desired specificity ... [i.e.,] for the purpose of detecting expression of the disease-related gene products"). Furthermore, Ghai et al discloses that "the cells can

be examined to determine whether one or more phenotypes has been altered to resemble a normal or wild type phenotype, or a phenotype more likely to produce a lower incidence or severity of symptoms" (see Ghai et al, column 4, lines 34-38).

For ***claims 28 and 30***, Ghai et al discloses binding antibodies to target cells wherein the target cells are "altered" as a result of the binding i.e., the conformation of the antigens displayed on the target cells are "altered" when bound by antibodies via non-covalent dipole-dipole, charge-dipole interactions, etc. (see Ghai et al, columns 19-22), which anticipates claim 28 because the type of "alteration" was not specified and the term "permitted" is vague and indefinite (see 35 U.S.C. 112, second paragraph rejection above). Furthermore, the isolation of target cell proteins and genes are always "permitted" since they were never "prevented" and, consequently, the addition of monoclonal antibodies continues to "permit" their isolation. In addition, Ghai et al discloses the use of antibodies bound to a solid-support that is used to isolate cells containing the genes related to a disease state and, consequently, "permits" the isolation of genes encoding said displayed protein or polypeptides. Finally, Ghai et al also reads on the limitation wherein "the target cell binds to one or more of the components of the complex" as well because it is not clear what applicant is referring to by "the complex" (see 35 U.S.C. 112, second paragraph rejection above) and because a "complex" is formed between antibody and antigen wherein the cell is attached to the antigen. Therefore, Ghai et al anticipates both claims 28 and 30.

For **claim 29**, Ghai et al discloses food and food like substances which bind to the target cells and subsequently modulate the production and/or cessation of a gene product,

which helps to identify the proper "displayed protein or polypeptides" and subsequently "permits" their recovery (see Ghai et al, see "Summary of the Invention", see especially column 2, last paragraph), which anticipates claim 29.

For **claim 31**, Ghai et al discloses "target cells" that contain genes associated with various "diseases" that would affect the viability of a living microorganism (see Ghai et al, columns 6-11, section for "Genes Associated with Diseases or Undesirable Conditions"), which anticipates claim 31.

For **claim 32**, Ghai et al discloses, "[a]ny type of cell can be used in the screening assays of the invention, including cells directly obtained from a subject, and cells that have been cultured in vitro and/or genetically engineered. The term "test cell" as used herein broadly encompasses cells or prokaryotic and eukaryotic organism such as bacteria, yeasts ...", which anticipates claim 32 (see also column 7, last paragraph, "in specific embodiments, the methods of the invention may be used to ... [treat] ... infectious diseases").

For **claim 34**, Ghai et al discloses the synthesis of "cell surface markers" on the target cell that are expressed as a function of the applied food or food like substances (see Ghai et al, column 20, first paragraph, "Separated cells can be directly deposited into individual wells of multi-well plates. These techniques are especially preferred if the disease-related gene products are expressed on the cell surface"), which anticipates claim 34.

For **claims 35-36**, Ghai et al discloses "[a]ny gene or functional nucleotide sequence ... which is associated with or related to the development, onset, progression or

other manifestation of any disease or undesirable condition in human or other animal ... is intended to fall within the scope of the present invention" would anticipate "RNA binding polypeptides" because said "RNA binding polypeptides" are associated with disease such as "HIV tat" and thus would fall within the scope of the invention disclosed by Ghai et al. Furthermore, "drug resistance enzyme" would also be encompassed by the invention disclosed by Ghai et al because the drug resistance enzymes are associated with disease "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). The Office does not have the facilities to make such a comparison and the burden is on the applicants to establish the difference. See *In re Best,* 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray*, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.).

For ***claims 37-39 and 42***, Ghai et al discloses a method for producing antibodies, chimeric antibodies and monoclonal antibodies against cells that contain genes that are associated with a disease wherein the level of production of said gene products is modulated by food or food substances (see Ghai et al, entire document, especially column 3, lines 41-52 and columns 20-21), which anticipates claim 37-39 and 42. In this scenario, the antibodies that are produced by the hybridoma cells and/or naturally occurring cells represent the "proteins or polypeptides" that are being "screened" and the collection of genes that encode said antibodies (and their hypervariable regions) represent the "gene library" that is produced after immunization. Selecting "favorable" hybridoma cells and/or natural cells after several rounds of "screening" results in the production of

antibodies, monoclonal antibodies and/or chimeric antibodies that bind to the "target cells" that contain the genes associated with disease (see Ghai et al, column 20, paragraph s, "Immunoassays and non-immunoassays for disease-related gene products or reporter molecules will typically comprise incubating a sample; such as a biological fluid, a tissue extract, freshly harvested cells, test cell conditioned culture media or test cell lysates, in the presence of a detectably labeled antibody capable of identifying disease-related gene product or reporter molecule, and detecting the bound antibody by any of a number of techniques well known in the art") (see also column 21, lines 16-29, "Antibody fragments which recognize specific epitopes may be generated by known techniques ... Fab expression libraries can be constructed to allow rapid and easy identification of monoclonal Fab fragments with the desired specificity ... [i.e.,] for the purpose of detecting expression of the disease-related gene products"). Furthermore, Ghai et al discloses that the "ligand" can be "modified" to "label" the synthesized proteins or polypeptides (see Ghai et al, section on "Screening Assays", especially column 21, last 3 paragraphs and column 22, first 6 paragraphs). Furthermore, Ghai et al discloses the use of ELISA technique, which anticipates claims 39 and 42 wherein the attached molecule can "initiate a labeling reaction" (see Ghai et al, column 21, lines 30-58).

Claim Rejections - 35 USC § 103

15. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

16. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

17. Claims 1-5, 7-8, 10-11, 15, 27-32, 34-39 and 42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ghai et al (US # 5,955,269) (Date of Patent: **Sep. 21, 1999**; Filed: **Jun. 20, 1996**) and Wagner (EP 0174753 A1) (Date of Publication: **March 19, 1986**).

For 1-5, 7-8, 10-11, 15, 27-32, 34-39 and 42, Ghai et al teaches all the limitations stated in the 35 U.S.C. 102(e) rejection above (incorporated in its entirety herein by reference), which anticipates claims 1-5, 7-8, 10-11, 15, 27-32, 34-39 and 42 and, consequently, also renders obvious claims 1-5, 7-8, 10-11, 15, 27-32, 34-39 and 42.

The prior art teachings of Ghai et al differ from the claimed invention as follows:

For **claim 33**, Ghai et al is deficient in that it does not specifically teach the use of a method wherein molecules produced by the cell result in the release of other molecules from liposomes.

For **claims 40**, Ghai et al is deficient in that it does not specifically teach a method wherein phospholipase C is attached to a ligand and liposomes are added after binding of the ligand to the cell or tissue surface such that phospholipase C results in release of the liposome contents.

For **claim 41**, Ghai et al is deficient in that it does not specifically teach the use of a method wherein the liposome contains streptavidin, HIV tat, signal recognition particle (SRP), an antibody (or fragment thereof), a specific mRNA or protein binding molecule, F pilus or nickel.

Wagner teaches the limitations that Ghai et al lacks:

For **claims 33, 40 and 41**, Wagner teaches an assay method wherein "one of the components used in the assay has an active sac lysing agent attached thereto, and another component in the assay is a sac, which has enclosed therein, a marker and sac lysing agent which is active for lysing sacs only when released from the sacs" (see Wagner, entire document, especially page 3, second paragraph), which reads on claim 40 because Wagner defined the "sacs" as "liposomes" (see Wagner, page 5, second paragraph and page 6, last two paragraphs) and defined the "marker" as "radioisotompes, enzymes, ... chromogen, a luminescent compound, a phosphorescent compound, spin labels [or other] detectable markers" (see Wagner, page 9 last paragraph and page 10, first paragraph). Furthermore, Wagner indicated that in a preferred embodiment the "tracer" molecules can be used in the assay wherein said tracer is "a ligand having a sac lysing agent in an active form", which would read on phospholipase C (see also, page 22, Example II).

It would have been obvious to one skilled in the art at the time the invention was made to make carry out the screening method of Ghai et al with the liposome detection method disclosed by Wagner because Wagner explicitly states that the liposome detection method can be used to replace standard immunoassays and the method of Ghai et al employs standard immunoassays (see Wagner, page 1, first 3 paragraphs). Furthermore, one of ordinary skill in the art would have been motivated to use the method of Ghai et al with the liposome detection method of Wagner because Wagner explicitly states that his detection method is more sensitive (see Wagner, page 2, paragraphs 2 and 3). Furthermore, one of ordinary skill in the art would have reasonably expected to be successful because Wagner teaches several successful examples of using liposome detection methods in similar assay methods (see Wagner, Examples I-III).

Status of Claims/Conclusion

18. No claims are allowed.

19. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

20. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon D Epperson whose telephone number is (703) 308-2423. The examiner can normally be reached Monday-Friday from 9:00 to 5:30.

21. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on (703) 306-3217. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 872-9307 for After Final communications.

22. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-2439.

Jon D. Epperson, Ph.D.

December 10, 2002

BENNETT CELSA
PRIMARY EXAMINER